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Linking cerebellar functional gradients to transdiagnostic behavioral dimensions of psychopathology

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ABSTRACT

High co-morbidity and substantial overlap across psychiatric disorders encourage a transition in psychiatry research from categorical to dimensional approaches that integrate neuroscience and psychopathology. Converging evidence suggests that the cerebellum is involved in a wide range of cognitive functions and mental disorders. An important question thus centers on the extent to which cerebellar function can be linked to transdiagnostic dimensions of psychopathology. To address this question, we used a multivariate data-driven statistical technique (partial least squares) to identify latent dimensions linking human cerebellar connectome as assessed by functional MRI to a large set of clinical, cognitive, and trait measures across 198 participants, including healthy controls (n = 92) as well as patients diagnosed with attention-deficit/hyperactivity disorder (n = 35), bipolar disorder (n = 36), and schizophrenia (n = 35). Macroscale spatial gradients of connectivity at voxel level were used to characterize cerebellar connectome properties, which provide a low-dimensional representation of cerebellar connectivity, i.e., a sensorimotor-supramodal hierarchical organization. This multivariate analysis revealed significant correlated patterns of cerebellar connectivity gradients and behavioral measures that could be represented into four latent dimensions: general psychopathology, impulsivity and mood, internalizing symptoms and executive dysfunction. Each dimension was associated with a unique spatial pattern of cerebellar connectivity gradients across all participants. Multiple control analyses and 10-fold cross-validation confirmed the robustness and generalizability of the yielded four dimensions. These findings highlight the relevance of cerebellar connectivity as a necessity for the study and classification of transdiagnostic dimensions of psychopathology and call on researcher to pay more attention to the role of cerebellum in the dimensions of psychopathology, not just within the cerebral cortex.

1. Introduction

Our understanding of cerebellar contributions to neurological function has changed from a traditional view focused on motor coordination, to a modern understanding that also implicates the cerebellum in a broad range of high-level cognitive and affective processes (Schmahmann et al., 2019). An increasing body of evidence also supports cerebellar involvement in a wide range of psychiatric disorders (Sathyanesan et al., 2019; Stoodley, 2016). Up to now, most psychiatric studies investigating the role of the cerebellum have been conducted based on categorical diagnostic criteria that view psychiatric disorders as independent entities (Caspi and Moffitt, 2018). It is increasingly

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recognized that existing clinical diagnostic categories might be suboptimal, as there is substantial overlap in symptoms, cognitive dysfunction and genetic factors across multiple psychiatric disorders(Caspi and Moffitt, 2018; Kotov et al., 2017). These overlaps can be reflected by shared neurobiological structure and function, and polymorphism abnormalities across psychiatric syndromes(Devlin et al., 2013; Goodkind et al., 2015; Janiri et al., 2020; McTeague et al., 2017). The high rates of comorbidity between psychiatric disorders and heterogeneity within one diagnostic group further exacerbates this problem (Chen et al., 2020; Feczko et al., 2019; Jacobi et al., 2004). This context has motivated transdiagnostic initiatives, such as the National Institute of Mental Health's Research Domain Criteria (Cuthbert, 2014), which encourages a transition in psychiatry research from categorical to dimensional approaches that integrate neuroscience and psychopathology (Cuthbert, 2014).

Recent clinical neuroscience studies have begun to adopt transdiagnostic approaches to highlight the importance of altered cerebellar structure in broad risk for psychopathology (Moberget et al., 2019; Romer et al., 2018; Romer et al., 2021). Previous animal and human neuroimaging studies have provided converging evidence for the involvement of cerebellar function in a wide range of behaviors that are dependent on circuits connecting the cerebellum with multiple cerebral cortical regions (Bostan et al., 2013; Caligiore et al., 2017; Kelly and Strick, 2003; Schmahmann et al., 2019). Accumulating evidence supports dysfunctional cerebellar connectivity in many psychiatric disorders, such as schizophrenia (Brady et al., 2019), bipolar disorder (Shinn et al., 2017), major depression (Jiang et al., 2019), attention-deficit/hyperactivity disorder (Kucyi et al., 2015) and autism (Stoodley et al., 2017). Moreover, study of clinical high-risk subjects demonstrate that dysconnectivity of cerebellar circuits can serve as a state-independent neural signature for psychosis prediction and characterization (Cao et al., 2018). Within this context, an understudied area of investigation is the extent to which cerebellar function can be linked to transdiagnostic dimensions of psychopathology.

Resting-state functional connectivity has been widely used to characterize disconnection mechanisms in many psychiatric disorders (Buckholtz and Meyer-Lindenberg, 2012; Sha et al., 2019), and is a promising tool for deepening our understanding of transdiagnostic dimensions (Elliott et al., 2018; Kebets et al., 2019; Xia et al., 2018). However, previous studies investigating functional connectivity-informed dimensions of psychopathology often ignore the importance of the cerebellum, e.g., by using a coarse delineation of the cerebellum with only a few regions of interest to represent the whole cerebellar information (Kebets et al., 2019; Xia et al., 2018). Recent developments in cerebellar functional mapping indicate that cerebellar functional organization can be characterized using macroscale spatial gradients of connectivity, a low dimensional continuous space that reflects the overarching spatial patterns that underpin the observed neural data (Guell et al., 2018). The principal connectivity gradient of cerebellar cortex captures a progression from sensorimotor to cognitive processing areas (Guell et al., 2018), similar to the organization of the cerebral cortex (Margulies et al., 2016; Mesulam, 1998). This low-dimensional representation of the principal axis of cerebellar macroscale functional organization thus provides a useful tool to characterize cerebellar function at the single-subject level which can then be correlated with single-subject behavioral measures. This approach offers an unprecedented opportunity to interrogate the relationship between cerebellar functional organization and behavioral measures of clinical phenomena, cognitive ability, and personality traits in mental health and disease.

In this study, we analyzed UCLA Consortium for Neuropsychiatric Phenomics open access dataset, a unique and large resting-state fMRI and behavioral dataset (Poldrack et al., 2016) using gradient-based and partial least squares, a multivariate data-driven statistical techniques with the objective to discover the latent dimensions that link cerebellar functional organization to behavioral measures spanning clinical, cognitive, and personality trait domains across healthy controls (HC), and patients with attention-deficit/hyperactivity disorder (ADHD), bipolar disorder (BD) and schizophrenia (SZ). This approach yielded dimensions that optimally linked co-varying cerebellar connectivity gradients and behavior in individuals across traditional diagnostic categories, in accordance with a transdiagnostic dimensional approach. Multiple control analyses were used to optimize the robustness of these latent dimensions. Furthermore, we performed 10-fold cross-validation to assess the generalization performance of latent dimensions to unseen test data. Importantly, cross-validation approaches can help guard against overfitting that arises from high dimensional neurobiological data (Yarkoni and Westfall, 2017).

2. Materials and methods

2.1. Participants

Data from the UCLA Consortium for Neuropsychiatric Phenomics (CNP) dataset (Poldrack et al., 2016) were downloaded from OpenNeuro (https://openneuro.org/datasets/ds000030/versions/00001). This dataset consists of neuroimaging and behavioral data from 272 right-handed participants, including both HC (n = 130) and individuals with neuropsychiatric disorders including SZ (n = 50), BD (n = 49), and ADHD (n = 43). Details about participant recruitment can be found in the original publication (Poldrack et al., 2016). Written informed consent was obtained from all participants and related procedures were approved by the Institutional Review Boards at UCLA and the Los Angeles County Department of Mental Health. Table 1 shows a summary of demographic and clinical information of the 198 participants who survived image preprocessing quality controls (see below).

2.2. Behavioral assessment

The CNP behavioral measures encompass an extensive set of clinical, personality traits, neurocognitive and neuropsychological scores (Table S1). Behavioral measures were excluded from the partial least squares (PLS) analysis when data was missing for at least 1 participant among the 198 participants. As a result, we included a set of 55 behavioral and self-report measures from 19 clinical, personality traits,

Table 1
Demographic characteristics of each diagnostic group.

Variables	ADHD	BD	HC	SZ	F or X^2	P value
Sample size	35	36	92	35		
Age (years, mean(SD))	31.40 (10.50)	34.44 (8.91)	30.50 (8.50)	35.54 (8.97)	3.51	1.6×10^{-2}
Male sex, n(%)	18 (51.4)	19 (52.8)	51 (55.4)	27 (77.1)	6.54	8.8×10^{-2}
Education (years, mean (SD))	14.43 (1.79)	14.64 (1.94)	15.26 (1.62)	12.71 (1.64)	18.75	1.0×10^{-10}
Site 1, n(%)	17 (48.6)	18 (50)	73 (79.3)	14 (40)	23.72	2.9×10^{-5}
Head motion, mean FD, mean(SD)	0.069 (0.04)	0.083 (0.05)	0.066 (0.03)	0.096 (0.04)	6.16	5.1×10^{-4}
Number of current medication use (mean (SD))	0.57 (1.14)	2.50 (1.93)	0(0)	2.20 (1.57)	57.19	1.6×10^{-26}
Number of substance use (mean(SD))	1.31 (1.68)	2.58 (2.09)	0.62 (1.10)	2.46 (2.23)	17.89	2.7×10^{-10}

Notes: Group differences were determined by either one-way ANOVA for continuous variables or chi-square tests for categorical variables. FD, framewise displacement; Number of substances use, including nicotine, alcohol, cannabis and other psychotropic substances. The degree of freedom for F test in ANOVA is 197. The degree of freedom of X^2 test is 3.

neurocognitive and neuropsychological tests in the PLS analysis. Table S2 summarized the behavioral measures for each group. Excluded 64 behavioral measures in PLS analysis were considered in post-hoc analyses (Table S3).

2.3. Data acquisition and image preprocessing

Resting-state functional and structural MRI data were collected on two 3T Siemens Trio scanners (Ahmanson-Lovelace Brain Mapping Center (Siemens version syngo MR B15) and the Staglin Center for Cognitive Neuroscience (Siemens version syngo MR B17)) at UCLA using the same acquisition parameters. Resting-state functional MRI data were collected using a T2*-weighted echoplanar imaging sequence with the following scan parameters: TR/TE = 2000 ms/30 ms, flip angle = 90°, matrix 64×64, field of view (FOV) = 192*192 mm^2, 34 interleaved slices, slice thickness = 4 mm, and oblique slice orientation. The resting fMRI scan lasted 304 s for each participant, and 157 volumes were acquired. During scanning, all participants were instructed to keep relaxed and keep their eyes open. Additionally, T1-weighted high-resolution anatomical data were acquired for each participant using an MPRAGE sequence (scan parameters: TR/TE = 1900 ms/2.26 ms, matrix = 256×256, FOV = 250*250 mm^2, sagittal plane, slice thickness = 1 mm, 176 slices). The anatomical data were used to normalize functional data. See Supporting Information for details.

Among the 272 participants, there were seven participants with missing T1 weighted scans, four participants were missing resting-state functional MRI data scans, and 1 participant had signal dropout in the cerebellum (Gorgolewski et al., 2017), thus only data from 260 participants were preprocessed. All preprocessing steps were consistent with our previous studies (Dong et al., 2019; Dong et al., 2020). In brief, the preprocessing steps included slice timing, realignment, normalization, wavelet despiking of head motion artifacts, regression of linear trend, Friston 24 head motion parameters, white matter and CSF signal, and filtering (0.01–0.1 Hz) (see supplementary methods for details). Because global signal may be an important neuroimaging feature in clinical populations (Hahamy et al., 2014), we did not conduct global signal regression (GSR) in our main analyses, but GSR was considered in control analysis. In addition, we excluded 42 participants due to head motion exceeding 1.5 mm or 1.5° rotation or with >10 % images showing framewise displacements >0.5 mm (Power et al., 2012) or mean FD >0.20 mm during MRI acquisition. Further, we further excluded 20 participants because of incomplete coverage of the cerebellum. This process left 198 participants as a final sample for our study, among which there were 35 ADHD, 36 BD, 92 HC and 35 SZ participants.

2.4. Cerebellar connectivity gradient extraction

We used diffusion map embedding (Coifman et al., 2005) to identify a low-dimensional embedding gradient from a high-dimensional intra-cerebellar cortex connectivity matrix for each participant. Diffusion embedding results in multiple, continuous maps ("gradients"), which capture the similarity of each voxel's functional connections along a continuous space. In other words, this data-driven analysis results in connectivity gradients that provide a description of the connectome where each voxel is located along a gradient according to its connectivity pattern. Gradient values represent information about the spatial pattern in the embedding space—shifts in value are not meaningful in terms of "higher" or "lower" scores, but rather reflect changes in relative similarity within a latent dimension, i.e., the similarity of functional connectivity patterns along each dimension ("gradient"). Then, we used an average connectivity matrix calculated from all participants to produce a group-level gradient component template. We then performed Procrustes rotation to align the gradients of each participant to this template (Langs et al., 2015). In order to maximize reliability, reproducibility, and interpretability, we only used the first gradient component in our analyses. The first gradient (or principal gradient) explains as much of the variance in the data as possible (~30 %, Fig. S1), represents a well-understood motor-to-supramodal organizational principle in the cerebellar and cerebro-cerebral connections, and has been shown to be reproducible at the single subject level, see representative individuals from each of the four groups in Fig. S2 (Guell et al. (2018); note that gradient 2 could not be reproduced as successfully as the principal gradient at the single-subject level). See supplementary methods for more details. Given the cerebellar functional gradients can be similarly constructed based on intra-cerebellar FC or cerebellar-cerebral FC in the literature, we also tested cerebellar gradient based on cerebellar-cerebral FC. Intra-cerebellar connectivity gradient analysis focuses on exploring the intrinsic organization of the cerebellum without involving its connectivity profiles with the cerebral hemispheres or other brain structures. The cerebellar-cerebral cortical gradients emphasize the communication between cerebellar and cerebral cortex. In addition, considering the well-established involvement of cortex and subcortical nuclei in higher-order cognitive function and psychiatric disorders, we also constructed the cerebellar gradient based on cerebellar-the rest of the brain (cerebral cortex + subcortical nuclei) FC. We reported the intra-cerebellar FC gradient (6242 voxels) as the main result, but also included cerebellar-cerebral, and cerebellar-the rest of the brain (cerebral cortex + subcortical nuclei) FC gradients in control analyses.

2.5. Partial least squares analysis

We applied PLS to investigate the relationship between cerebellar connectivity gradient and behavioral measures across diagnostic categories. PLS is a multivariate statistical technique that derives latent variables (LVs), by finding weighted patterns of variables from two given data sets that maximally covary with each other (Krishnan et al., 2011; McIntosh and Mišić, 2013). Each LV is comprised of a cerebellar connectivity gradient pattern at voxel level ("gradient saliences") and a behavioral profile ("behavioral saliences"). Individual-specific cerebellar gradient and behavioral composite scores for each LV were obtained by linearly projecting the gradient and behavioral measures of each participant onto their respective saliences. See supplementary methods for mathematical details. Because mean framewise displacement (FD) was negatively correlated with several behavioral measures and there were significant differences in age, sex, education, site, and mean FD across groups (Table 1), we regressed out these confounding effects from both behavioral and cerebellar gradient data before PLS analysis.

In order to evaluate the significance of the LVs, we applied permutation testing using 1000 permutations for behavioral data and repeating the PLS analysis to determine the null distribution of the singular values. Considering significant group differences in various behavioral measures (Table S2), the permutation procedure was performed within each primary diagnostic group. Our results of interest were the top five LVs which explained at least 5 % of covariance between cerebellar gradients and behavioral measures (see Fig. S2). We applied a false discovery rate (FDR) correction of $q < 0.05$ on the permuted p-values of the five LVs to control for multiple comparisons.

To assess the contribution of a given gradient voxel or behavior to a given LV, we computed correlations between the original measure (gradient voxel or behavior) and the corresponding composite scores (Courville and Thompson, 2001; Sherry and Henson, 2005). A large correlation value (i.e., large weight, positive or negative) for a given measure (behavioral or gradient voxel) for a given LV indicates greater contribution of the behavior or gradient voxel to the LV. Then, the confidence intervals for these correlations were determined a by bootstrapping procedure that generated 500 samples with replacement from the original gradient and behavioral data. Considering significant diagnostic differences in many behavioral measures (Table S2), we took diagnostic groups into account within each bootstrap sample. To

identify variables (gradient voxels or clinical measures) that make a significant contribution to the overall pattern, we calculated Bootstrapped Z scores as the ratio of each variable's correlation coefficient (i.e., weight) to its bootstrap-estimated standard error. Then, we converted the Z scores to p values, which were FDR corrected ($q < 0.05$).

To test the generalizability of each LV, we used a 10-fold cross-validation of the PLS analysis with 200 repetitions. Importantly, the cross-validation approach can help to guard against overfitting that arises from high dimensional neurobiological data (Yarkoni and Westfall, 2017). Specifically, first, we assigned 90 % of the participants (within each primary diagnostic group) to the training set and the remaining 10 % of participants (within each primary diagnostic group) to the test set. For each training set, PLS was used to estimate gradient and behavioral saliences (i.e., U_{train} and V_{train}). Next, the test data were projected onto the gradient and behavioral patterns derived from the training set. This allowed us to estimate individual-specific gradient and behavior composite scores and their correlation for the test sample (i.e. $corr(X_{test}U_{train}, Y_{test}V_{train})$) for LVs 1–4. This procedure was repeated 200 times to make sure the results are not biased by the initial split. Finally, we used a permutation test (behavioral data shuffled 1000 times within each diagnostic group) to assess the significance of these correlation coefficients.

If a given LV was statistically significant, we performed one-way ANOVA to test whether cerebellar gradient and behavioral composite scores of this LV were different among different diagnoses, if significant, least significant difference (LSD, in SPSS) post hoc tests were performed, which would help interpret the significant function of this LV. It should be noted that the present objective was not to find commonalities and distinctions in the cerebellar-psychopathology relationship across the three diagnoses. In addition, we furthermore tested whether the composite scores for significant LVs were correlated with medication load (number of medications current use) and substance use (number of substances use, including nicotine, alcohol, cannabis and other psychotropic substances) by performing Pearson's correlations analyses. Given the exploratory nature of medication and substance use effect analysis in our study, we only consider the number of medications or substance current use, it should keep caution when interpreting these results. For binary measures, we used T tests, and for continuous measures, we used Pearson's correlations. FDR correction ($q < 0.05$) was applied to these association analyses.

False discovery rate (FDR) correction ($q < 0.05$) was applied to all analyses.

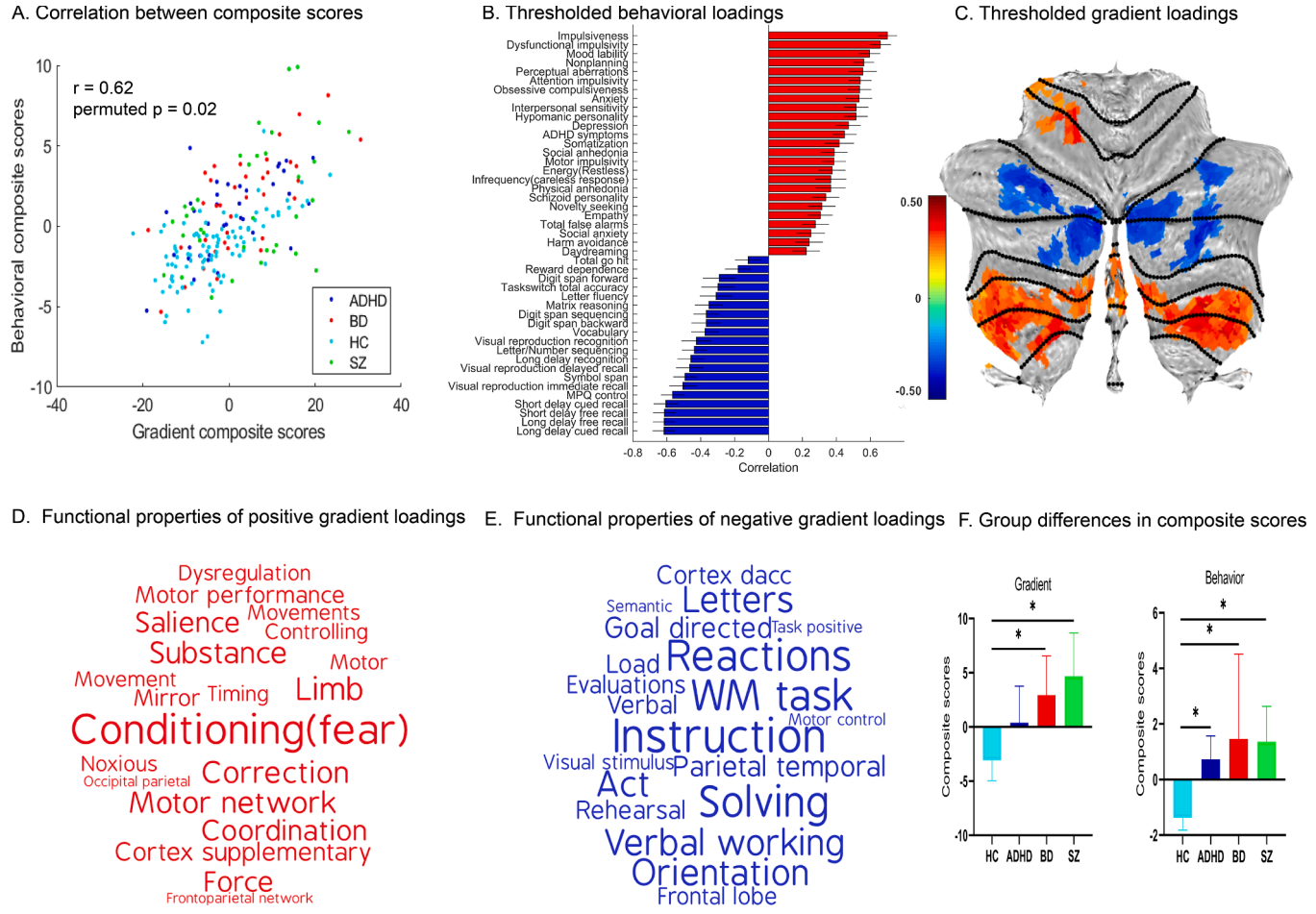

Fig. 1. Latent variable 1: general psychopathology. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV1. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard errors. (C) Significant gradient pattern associated with LV1. The contribution of each voxel is measured by correlation between participants' cerebellar gradient scores and the corresponding cerebellar gradient composite scores (FDR correction, $q < 0.05$). Gradient pattern displayed on cerebellar flat maps were generated using the SUIT toolbox (http://www.diedrichsenlab.org/imaging/suit.htm). (D) Functional properties of positive gradient loadings. (E) Functional properties of negative gradient loadings. (F) Group differences in cerebellar connectivity gradient and behavioral composite scores. Significant differences are indicated by asterisks (FDR correction, $q < 0.05$). Error bars indicate standard deviation.

2.6. Decoding the general meaning of higher/lower cerebellar gradient composite score in each LV

To understand meaning of an individual with high/low gradient composite score, we calculated and visualized the average map of gradient for individuals in the top and bottom third of gradient composite scores, and also calculated the difference (Mckeown et al., 2020).

2.7. Meta-analytic decoding of the function of significant gradient loadings using NeuroSynth

We used a large-scale database-informed *meta*-analytic approach as implemented in NeuroSynth (Yarkoni et al., 2011) to decode the functional properties of significant gradient loadings in LV1-LV4. The top 20 terms showing the highest correlations for significant positive or negative loadings mask were extracted, and the terms corresponding to each significant positive or negative loadings mask were visualized as a word cloud (Figs. 1-4D&E). The font size of the term in each word cloud is proportional to the correlation strength. However, the corresponding functional properties should be interpreted cautiously given its nature of exploratory.

2.8. Control analyses

We tested whether LVs were robust to global signal regression, total cerebellar grey matter volume regression, cerebellar gradients based on cerebellar-cerebral and cerebellar-the rest of the brain (cerebral cortex + subcortical nuclei) FC, adding confounding variables (age, sex, education, site, and head motion) into the behavioral data for the PLS analysis, non-Gaussian distributions of the behavioral data, diagnostic factors (HCs and patients separately), and site factors (each site separately). To assess the robustness of each LV, we computed Pearson's correlations between cerebellar gradient (or behavioral) saliences obtained in each control analysis and cerebellar gradient (or behavioral) saliences from the original PLS analysis. Finally, to confirm that each diagnostic group contributed the same amount to the overall composite correlations, we used the Fisher r-to-z transformation to compare the pairwise r-values (Diedenhofen and Musch, 2015). See supplementary methods for details.

2.9. Data and code availability

All data are freely provided by from the UCLA Consortium for Neuropsychiatric Phenomics (CNP)[34] available from OpenNeuro (https://openneuro.org/datasets/ds000030/versions/00001). Cerebellar

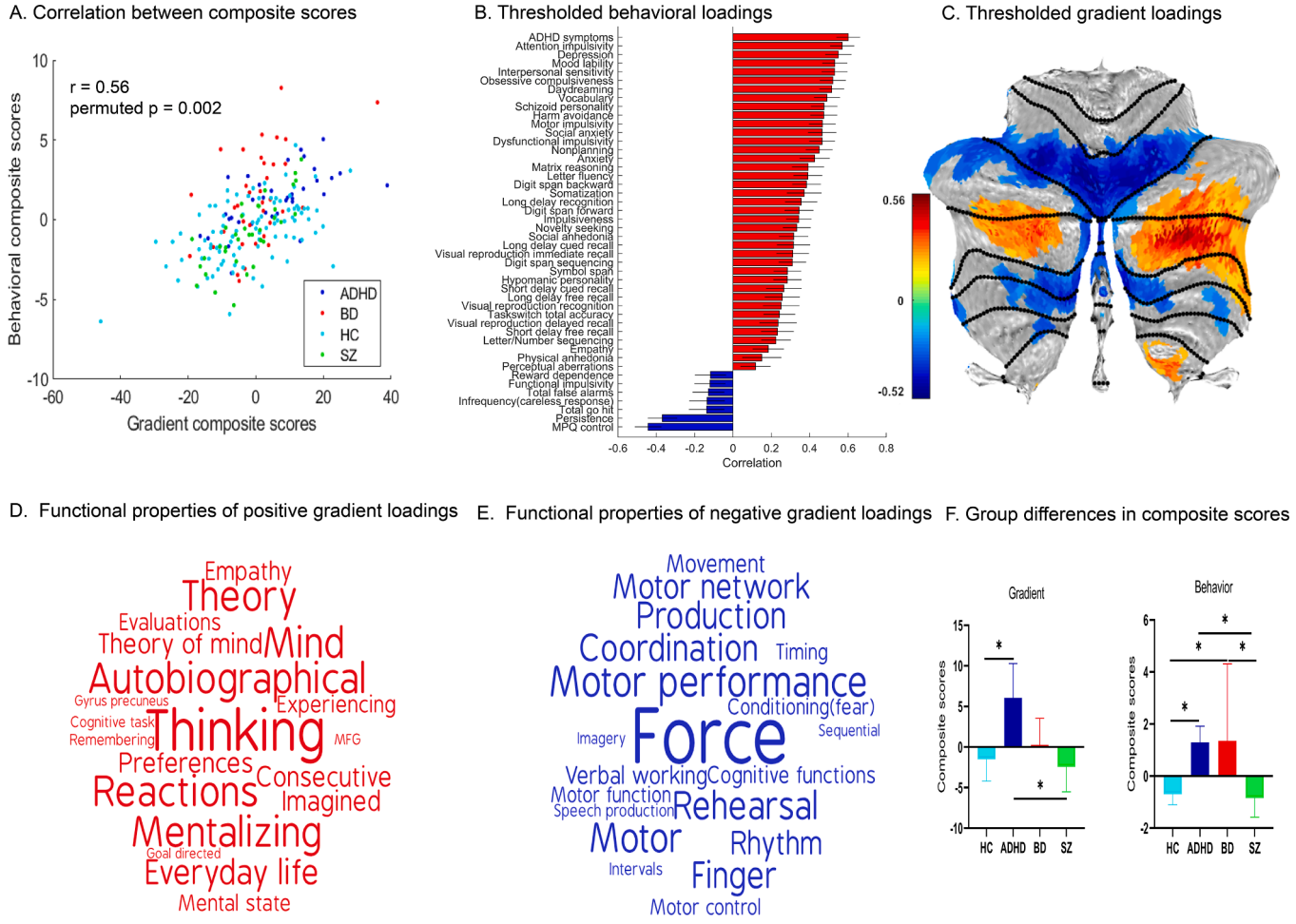

Fig. 2. Latent variable 2: impulsivity and mood. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV2. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard errors. (C) Significant gradient pattern associated with LV2. The contribution of each voxel is measured by correlations between participants' cerebellar gradient scores and the corresponding cerebellar gradient composite scores (FDR correction, $q < 0.05$). (D) Functional properties of positive gradient loadings. (E) Functional properties of negative gradient loadings. (F) Group differences in cerebellar connectivity gradient and behavioral composite scores. Significant differences are indicated by asterisks (FDR correction, $q < 0.05$). Error bars indicate standard deviation.

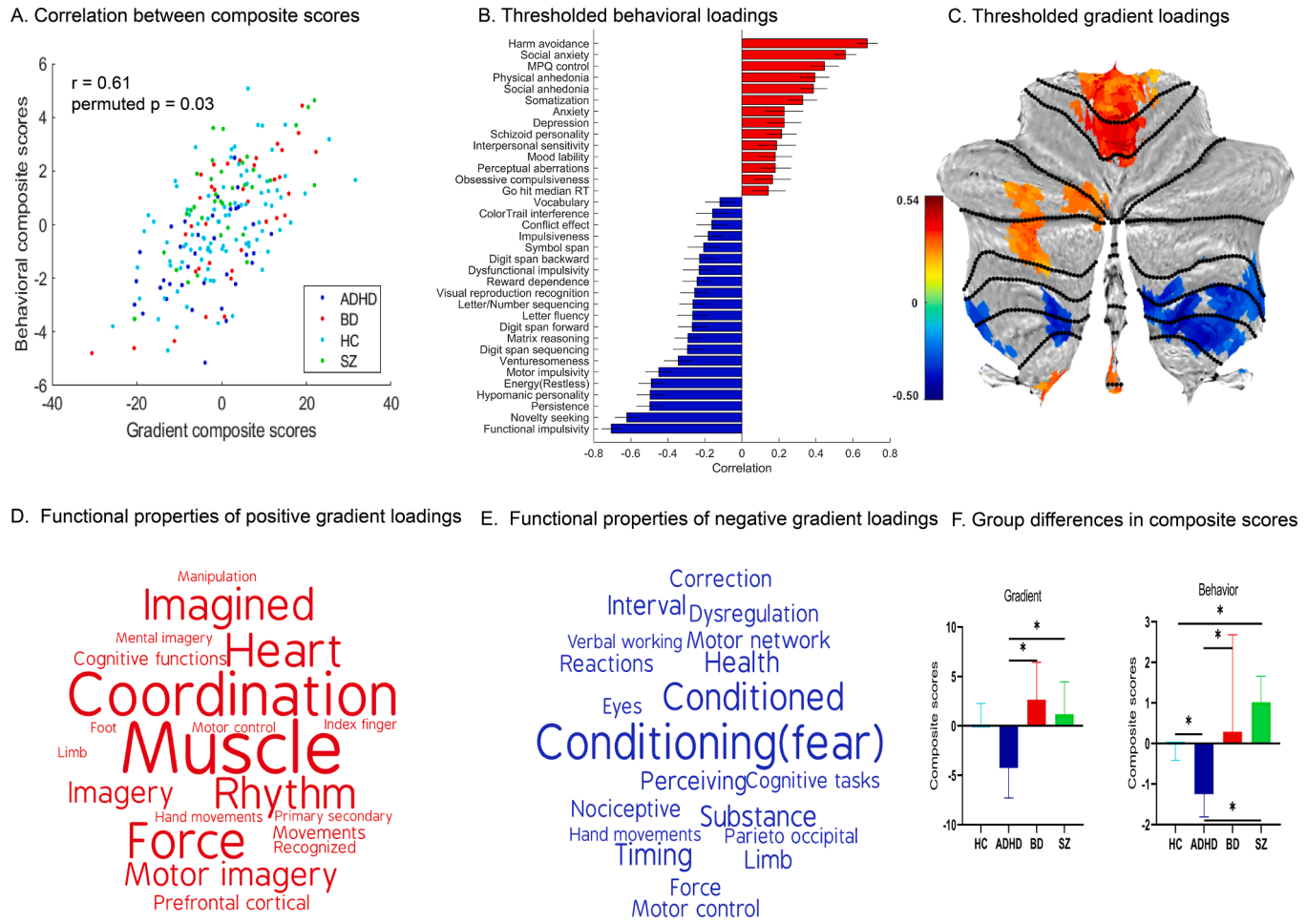

Fig. 3. Latent variable 3: internalizing and less externalizing symptoms. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV3. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard errors. (C) Significant gradient pattern associated with LV3. The contribution of each voxel is measured by correlations between participants' cerebellar gradient scores and the corresponding cerebellar gradient composite scores (FDR correction, $q < 0.05$). (D) Functional properties of positive gradient loadings. (E) Functional properties of negative gradient loadings. (F) Group differences in cerebellar connectivity gradient and behavioral composite scores. Significant differences are indicated by asterisks (FDR correction, $q < 0.05$). Error bars indicate standard deviation.

connectivity gradients were constructed by BrainSpace toolbox (Vos de Wael et al. (2020)https://github.com/MICA-MNI/BrainSpace). We used the Matlab code from https://github.com/danizoeller/myPLS (Zöller et al., 2017) and https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/disorder_subtypes/Kebe ts2019_TransdiagnosticComponents (Kebets et al., 2019), based on (Krishnan et al., 2011) to implement the PLS calculating.

3. Results

3.1. Four robust LVs linking cerebellar gradients and behavior

PLS correlation analysis revealed five significant latent variables (LVs) that reflect the direct covariant mapping between cerebellar connectivity gradients and behavioral measures. Since the fifth LV did not show robustness in control analyses as detailed in Table S4, we only focused on the first four LVs (LV1: $r = 0.62$, permuted $p = 2.0\text{x}10^{-2}$; LV2: $r = 0.56$, permuted $p = 2.0\text{x}10^{-3}$; LV3: $r = 0.61$, permuted $p = 3.0\text{x}10^{-2}$; LV4: $r = 0.60$, permuted $p = 1.2\text{x}10^{-2}$; Figs. 1-4A). The variance explained by each LV was 19.5 %, 13.7 %, 8.8 % and 6.0 %, respectively (Fig. S3). Importantly, 10-fold cross-validation confirmed generalizability (i.e. robustness of results in new data) of the first four LVs, as indicated by significant correlation between cerebellar gradient and behavioral composite scores in the test folds (LV1, $r = 0.21$, $p = 2.5\text{x}10^{-3}$; LV2, $r = 0.27$, $p = 2.1\text{x}10^{-3}$; LV3, $r = 0.22$, $p = 2.3\text{x}10^{-3}$; LV4, $r = 0.16$, $p = 2.5\text{x}10^{-3}$). Furthermore, the four LVs were robust to GSR and total cerebellar grey matter volume regression, as indicated by the high correlation ($r > 0.83$) between saliences of original PLS and PLS with GSR or total cerebellar grey matter volume regression. In addition, each diagnostic group contributed similarly to the overall composite correlations of these four LVs (FDR $q > 0.05$ for all pairwise comparisons, see Table S5). We also found that age, sex, education, site, or FD were not associated with any LV (Table S6).

Considering significant group differences in many behavioral measures (Table S2), we took diagnostic groups into account for the permutation procedure, bootstrapping procedure and cross-validation in the main text. However, when ignoring diagnostic groups (regarding all participants as one group), the results remained almost unchanged. See supplementary results and Figs. S4-S7 for details.

3.2. LV1: General psychopathology

The main contributors of behavior to LV1 were overall associated with greater psychopathology, e.g., higher impulsiveness, mood lability, dysfunctional impulsivity, anxiety, depression, somatization, social/physical anhedonia (Fig. 1B) and psychotic symptoms (Table S3)

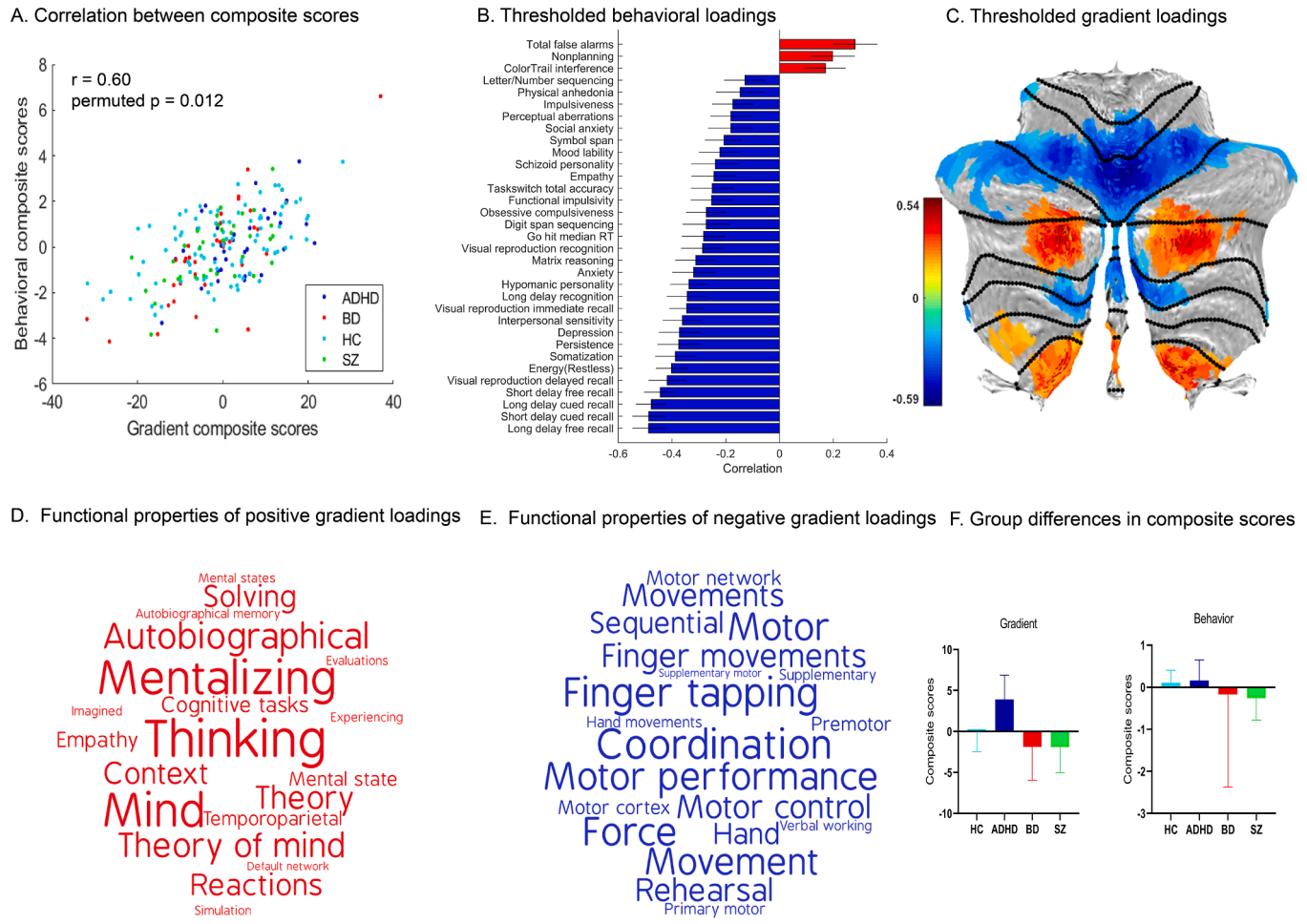

Fig. 4. Latent variable 4: executive dysfunction. (A) Correlation between cerebellar connectivity gradient and behavioral composite scores of participants. (B) Significant behavioral features associated with LV4. The contribution of each behavior is measured by correlations between participants' behavioral scores and the corresponding behavioral composite scores. Error bars indicate bootstrapped standard errors. (C) Significant gradient pattern associated with LV4. The contribution of each voxel is measured by correlations between participants' cerebellar gradient scores and the corresponding cerebellar gradient composite scores (FDR correction, $q < 0.05$). (D) Functional properties of positive gradient loadings. (E) Functional properties of negative gradient loadings. (F) Group differences in cerebellar connectivity gradient and behavioral composite scores. There were no significant differences among diagnostic groups in LV4 (FDR correction, $q < 0.05$). Error bars indicate standard deviation.

including mania, delusions and hallucinations; in addition to worse high-order cognitive control (e.g., working memory). As can be seen from Fig. 5A, individuals with higher gradient composite score showed increased shared connectivity similarity (lower functional differentiation) between the sensorimotor and supramodal cognitive systems. LV1 included positive weight in cerebellar lobules V, VI, VIIIA and VIIIB and negative weight in Crus I and II (Fig. 1C). The parts of significant positive weights were generally related to stimulus induced external stimuli induced response functions (e.g., fear, salience and substance, Fig. 1D), and the parts of significant negative weights were generally related to gold-directed functions (instruction, working memory, solving, Fig. 1E). One-way ANOVA revealed that there were significant differences in cerebellar gradient ($F = 6.630$, $df = 197$, $p < 0.001$) and behavioral composite scores ($F = 15.365$, $df = 197$, $p < 0.001$) among different diagnoses. Notably, post hoc tests observed that both cerebellar gradient and behavioral composite scores were higher in all diagnostic groups when compared with HCs (Fig. 1F; all differences were statistically significant except for ADHD). Exploratory analyses indicated that higher cerebellar gradient and behavioral composite scores in LV1 were associated with greater medication load. There was no significant association between LV1 composite scores and substance use (Table S6). Our interpretation is that LV1 is associated mainly with general psychopathology and high-order cognitive control deficits and is associated with diminished differentiation between sensorimotor and supramodal cognitive systems (see discussion).

3.3. LV2: Impulsivity and mood

The main contributors of behavior to LV2 were mainly involved in a mixture of impulsivity and mood, e.g., higher ADHD symptoms, attention impulsivity, depression, mood lability, interpersonal sensitivity, daydreaming and social anxiety, and lower control ability and persistence (Fig. 2B). As can be seen from Fig. 5A, individuals with higher gradient composite score showed decreased shared connectivity similarity (higher functional segregation) between the sensorimotor and supramodal cognitive systems. LV2 included positive weight in cerebellar Crus I, II and lobule IX and negative weight in lobules VI, VIIB and VIIIA (Fig. 2C). The parts of significant positive weights were generally related to self-related functions (e.g., thinking, autobiographical and mind, Fig. 2D), and the parts of significant negative weights were generally related to coordination functions (force, motor and coordination, Fig. 2E). One-way ANOVA revealed that there were significant differences in cerebellar gradient ($F = 4.109$, $df = 197$, $p = 0.007$) and behavioral composite scores ($F = 13.525$, $df = 197$, $p < 0.001$) among different diagnoses. Notably, patients with ADHD had the highest cerebellar gradient composite scores for LV2 (Fig. 2F). Post hoc tests

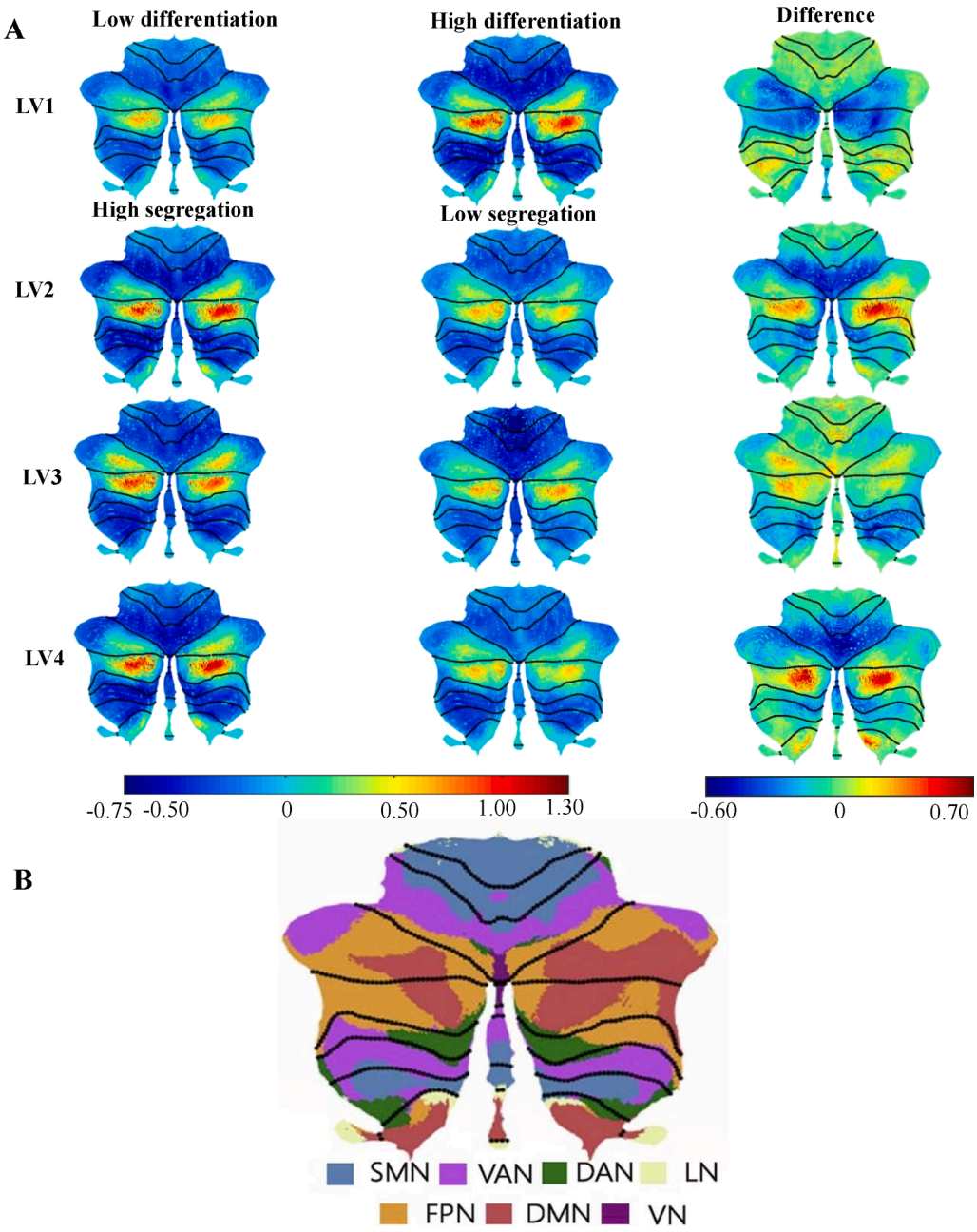

Fig. 5. (A) Lower functional differentiation (LV1) or higher functional segregation (LV2-4) between sensorimotor and supramodal cognitive systems was observed in individuals with higher cerebellar gradient composite scores. Left panel: group-averaged maps for high (top) and low (middle) similarity scores for cerebellar gradient as well as the difference between these groups (right). The right color bar reflects the scale of the high and low cerebellar gradient group-averaged maps while the left color bar reflects the scale of the difference map. Individuals with high gradient composite scores showed lower functional differentiation between sensorimotor (blue) and supramodal cognitive systems (yellow to red). The proximity of colors reflects greater similarity in connectivity patterns between regions. (B) Cerebellar representations of cerebral cortical resting-state networks based on Buckner et al. (2011). SMN, somatomotor network; VAN, ventral attention network; DAN, dorsal attention network; LN, limbic network; FPN, frontal-parietal network; DMN, default mode network; VN, visual network.

revealed that behavioral composite scores were significantly higher in patients with ADHD or BD than in HC and patients with SZ and cerebellar gradient composite scores were significantly higher in patients with ADHD than in HC and patients with SZ. There was no significant association between composite scores and medication load or substance use (Table S6). Our interpretation is that LV2 is associated mainly with inadequate attention regulation and is associated with the lack of efficient information integration between sensorimotor and supramodal cognitive systems (see discussion).

3.4. LV3: Internalizing and less externalizing symptoms

The main contributors of behavior to LV3 were mainly correlated with behavioral measures related to internalizing symptoms, e.g., higher harm avoidance, social anxiety, control, anhedonia, and somatization, and less externalizing symptoms, e.g., functional and motor impulsivity as well as novelty seeking (Fig. 3B). As can be seen from Fig. 5A, individuals with higher gradient composite score showed decreased shared connectivity similarity (higher functional segregation) between the sensorimotor and supramodal cognitive systems. LV3 included positive weight in cerebellar anterior vermis (I-VI) and negative weight in left Crus I, II, as well as lobules VIIIA and VIIIB (Fig. 3C). The parts of significant positive weights were generally related to coordination functions (e.g., muscle, coordination and rhythm, Fig. 3D), and the parts of significant negative weights were generally related to external stimulus induced response functions (e.g., fear, substance and perceiving, Fig. 3E). One-way ANOVA revealed that there were significant differences in cerebellar gradient ($F = 3.028$, $df = 197$, $p = 0.031$) and behavioral composite scores ($F = 8.273$, $df = 197$, $p < 0.001$) among different diagnoses. Post hoc tests revealed that cerebellar gradient and behavioral composite scores were significantly higher in patients with BD or SZ when compared with patients with ADHD (Fig. 3F), and behavioral composite scores were significantly higher in patients with SZ when compared with HC group. In addition, ADHD groups had lower

behavioral composite scores than HC group. Higher cerebellar gradient and behavioral composite scores were associated with greater medication load (Table S6). There was no significant association between LV3 composite scores and substance use (Table S6). Our interpretation is that LV3 is associated mainly with higher internalizing symptoms and lower externalizing behavior and is generally associated with the lack of efficient information integration between sensorimotor and supramodal cognitive systems (see discussion).

3.5. LV4: Executive dysfunction

The main contributors of behavior to LV4 included worse performance in multiple executive function domains, as well as with less somatization, interpersonal sensitivity and depression (Fig. 4B). As can be seen from Fig. 5A, individuals with higher gradient composite score showed decreased shared connectivity similarity (higher functional segregation) between the sensorimotor and supramodal cognitive systems. LV4 included positive weight in Crus I, II and lobules IX and negative weight in lobule VI (Fig. 4C). The parts of significant positive weights were generally related to self-related functions (e.g., thinking, autobiographical mentalizing and mind, Fig. 4D), and the parts of significant negative weights were generally related to coordination functions (motor, coordination and movements, Fig. 4E). One-way ANOVA revealed that there were not significant differences in cerebellar gradient ($F = 2.219$, $df = 197$, $p = 0.087$) and behavioral composite scores ($F = 0.693$, $df = 197$, $p = 0.557$) among different diagnoses (Fig. 4F). There was no significant association between composite scores and medication load or substance use (Table S6). Our interpretation is that LV4 is associated mainly with executive dysfunction and is generally associated with the lack of efficient information integration between sensorimotor and supramodal cognitive systems (see discussion).

3.6. Control analyses

Additional control analyses ensured the robustness of the first four LVs to cerebellar gradients based on cerebellar-cerebral FC, confounding variables, non-Gaussian distributions of the behavioral data, diagnostic factors (HCs and patients separately), and site factors (each site separately) (see supplemental results). It should be noted that when using cerebellar gradient based on cerebellar-cerebral FC or cerebellar-the rest of the brain (cerebral cortex + subcortical nuclei) FC, results were similar to the original PLS using the cerebellar gradient based on intra-cerebellar FC. Correlations between the saliences of the new and the original PLS analysis for the first four LVs ranged from 0.76 to 0.99, suggesting high correlation (Table S4) and ensuring the robustness of the first four LVs to the different methods to construct cerebellar gradient. Results of PLS using only control individuals or only patients demonstrated moderate to high correlations with original saliences for the first four LVs. However, correlations dropped to 0.14 and 0.22 for LV5 (Table S4); hence we did not describe LV5.

4. Discussion

Although the importance of cerebellar function in mental health and disease is increasingly recognized, the degree to which cerebellar connectivity is associated with transdiagnostic behavioral dimensions of psychopathology remains largely unknown. Leveraging a unique dataset including resting-state fMRI and behavioral assessments spanning clinical, cognitive, and personality traits, we found robust correlated patterns of cerebellar connectivity gradients and behavioral measures that could be represented in four transdiagnostic dimensions. Each dimension was associated with a unique spatial pattern of cerebellar connectivity gradients, and linked to different clusters of behavioral measures, supporting that individual variability in cerebellar functional connectivity can capture variability along multiple behavioral dimensions across psychiatric diagnoses. Our findings highlight the relevance of cerebellar neuroscience as a central piece for the study and classification of transdiagnostic dimensions of psychopathology.

4.1. Linking cerebellar functional gradients to transdiagnostic dimensions of psychopathology

A large body of literature has shown cerebellar functional abnormalities in mental disorders (Sathyanesan et al., 2019; Stoodley, 2016). New trends in psychiatry focus on transdiagnostic dimensions of psychopathology (Caspi and Moffitt, 2018; Insel et al., 2010). The present study is the first to link both approaches.

Adopting a transdiagnostic approach, three influential studies analyzing brain structure showed that alterations in cerebellar structure is associated with broad risk for psychopathology (Moberget et al., 2019; Power et al., 2012; Romer et al., 2018). However, these studies focused on clinical symptoms or cognitive function. The broader set of behavioral phenotypes in the present study allowed us to explore other dimensions of psychopathology, not constrained within the limits of clinical symptoms commonly investigated in many transdiagnostic studies (Elliott et al., 2018; Kaczkurkin et al., 2018; Kaczkurkin et al., 2019; Romer et al., 2018; Romer et al., 2021; Xia et al., 2018). Prior cerebellar structure studies using factor analyses suggested the presence of latent dimensions of psychopathology such as internalizing symptoms, externalizing symptoms, and psychosis symptoms (Lahey et al., 2017), as well as a general psychopathology (or p) factor (Lahey et al., 2012). While these dimensions are reliable and reproducible, they are entirely derived from clinical assessments, not informed by brain-based data such as fMRI functional connectivity. More broadly, previous studies investigating functional connectivity-informed dimensions of psychopathology often ignore the importance of the cerebellum, e.g., by using a coarse delineation of the cerebellum with only a few regions of interest to represent the whole cerebellar information (Kebets et al., 2019; Xia et al., 2018). These limitations were overcome in the present investigation. Further, compared to methods that focus on a single view (such as factor analysis applied on clinical data), the present study derived behavioral dimensions from co-varying individual differences in connectivity gradients and behavioral measures. This approach resonates with the Research Domain Criteria research framework that encourages the integration of many levels of information (Insel et al., 2010).

Our study indicates that individual variability in cerebellar functional connectivity gradient organization captures variability along multiple behavioral dimensions across mental health and disease. The associations with diverse dimensions of psychopathology were expected based on the consensus that the cerebellum is involved in virtually all aspects of behavior in health and disease[1]. In 1998, Mesulam proposed that brain regions can be organized along a gradient ranging from sensory-motor to higher-order brain processes (Mesulam, 1998). In line with Mesulam, most of the variance of cerebellar RSFC resembles a gradient that spans from primary sensory-motor cortices to high–order transmodal regions of the default-mode network (Guell et al., 2018). This principal gradient may thus represent one fundamental principle driving a hierarchical organization of cerebellar motor, cognitive, and affective functions. Here we show for the first time that there is a link between this principal gradient of cerebellar organization and behavioral measures across individuals with and without diagnoses of cognitive or affective disease.

4.2. Interpreting the functional significance of each latent variable

The most significant finding of the present investigation is the demonstration of an association between individual variations in cerebellar functional gradient values and multiple behavioral measures across mental health and diseases. As other brain-behavior association studies using multivariate analysis based on machine learning (Kohoutová et al., 2020), while it is not possible to provide a definitive

characterization of the functional significance of each LV based on the analyses presented here, we here present only one possible line of interpretation.

In LV1, greater behavioral composite score was associated with greater behavioral measures that we interpreted as general psychopathology and higher-cognitive control disabilities (including impulsiveness, mood lability, dysfunctional impulsivity, anxiety, depression, somatization, social/physical anhedonia and psychotic symptoms including mania, delusions and hallucinations). In line with the interpretation of LV1 as general psychopathology, both cerebellar gradient and behavioral composite scores were higher in all diagnostic groups when compared with HCs. Factor-analytic studies of multiple symptoms and diagnoses suggest that the structure of mental disorders can be summarized by three factors: internalizing, externalizing, and thought disorders (e.g., Lahey et al., 2017). The empirical observation that even these three transdiagnostic latent factors are positively correlated (Wright et al., 2013) has given rise to a more radical hypothesis, which is that there is the general psychopathology (or p) factor (Lahey et al., 2012), which is thought to reflect individuals' susceptibility to develop "any and all forms of common psychopathologies"(Caspi et al., 2014). The p factor has been extended to index functional impairment, negative affect, emotion dysregulation, and cognitive deficits (e.g., attention and memory problems) (for a review Caspi and Moffitt (2018)). In addition, the parts of significant cerebellar positive weights were generally related to stimulus induced external stimuli induced response functions (e.g., fear, salience and substance), and the parts of significant cerebellar negative weights were generally related to gold-directed functions (instruction, working memory, solving). Collectively, LV1 may thus reflect the p factor widely discussed in transdiagnostic cohorts (Lahey et al., 2012).

In LV2, greater behavioral composite scores were predominantly correlated with greater scores in areas related to impulsivity and mood including ADHD symptoms and attention impulsivity. Importantly, patients with ADHD had the highest gradient composite scores. LV2 might thus capture inattention and impulsivity/hyperactivity symptoms which characterize ADHD. However, other dimensions such as depression, mood lability and schizoid personality were also included in LV2, which makes this LV more likely to be a mixture of impulsivity and mood.

In LV3, greater behavioral composite scores were dominantly correlated with greater behavioral measures related to internalizing symptoms (including harm avoidance, social anxiety, control, and anhedonia) and lower externalizing symptoms (including functional and motor impulsivity, novelty seeking, and hypomanic personality). In addition, we found the parts of significant cerebellar positive weights were generally related to coordination functions (e.g., muscle, coordination and rhythm), and the parts of significant cerebellar negative weights were generally related to external stimulus induced response functions (e.g., fear, substance and perceiving). Combining these evidence, LV3 may thus reflect an internalizing vs externalizing factor (Lahey et al., 2017; Wright et al., 2013).

LV4 was predominantly associated with negative correlations with behavioral measures, most strongly in the executive functions (long delay free recall, short delay cued recall, long delay cued recall, short delay free recall, and visual reproduction delayed recall). LV4 might thus dominantly reflect executive dysfunction, although other behavioral domains also played a significant role in the behavioral composition of LV4 including restlessness, somatization, and persistence.

In the present study, we found that individuals with higher behavioral (general psychopathology) composites in LV1 have diminished differentiation between the sensorimotor and supramodal cognitive systems within cerebellar functional principal gradient organizations across psychiatric diagnoses, which is conceptually consistent with our previous studies (Dong et al., 2020; Dong et al., 2021) and other researcher (Elliott et al., 2018). In our previous studies, we found schizophrenia patients showed diminished differentiation in intra-cerebellar, cerebellar-cerebral gradient and cerebral-cerebral gradient. Functional principal gradient organizations in the brain have been proposed to reflect an architecture that optimizes the balance of externally and internally oriented functioning (Mesulam, 1998). In gradient organization, association areas are located at maximal distance from regions of primary areas that are functionally specialized for perceiving and acting in the here and now, supporting cognition and behavior not constrained by the immediate environment (Murphy et al., 2018; Murphy et al., 2019; Wang et al., 2019). The intricate neuronal circuitry of the cerebellum has been hypothesized to function as a "forward controller," creating internal models of how a given behavioral output will dynamically fit with contextual information (Ito, 2008), which is critical for monitoring and coordinating information processing in the service of mental processes (Andreasen et al., 1998; Schmahmann et al., 2019; Schmahmann and Sherman, 1998). Therefore, the diminished network differentiation would unavoidably result in ineffective functional specialization, leading to a blurred boundary between externally oriented immediate environment and internally abstract cognitive processing (Murphy et al., 2018; Northoff and Duncan, 2016), which might reflect an imbalance of externally and internally oriented functioning.

Regarding LV2-4, individuals with higher behavioral composites have higher functional segregation between the sensorimotor and supramodal cognitive systems within cerebellar functional principal gradient organizations across psychiatric diagnoses. The effective brain function is supported by the maintenance of subnetworks segregation as well as their integration (Wig, 2017). Therefore, higher functional segregation may contribute to the inefficient integration of bottom-up sensory information with top-down processes.

Notably, Kebets and colleagues investigated RSFC-informed dimensions of psychopathology in the CNP dataset (Kebets et al., 2019), focusing on connectivity within and between cerebral and subcortical areas and derived a general psychopathology variable similar to LV1 in our study (other LVs were different), indicating that cerebral and cerebellar analyses might offer complementary information regarding the relationship between brain activity and behavioral measures. Future studies analyzing both cerebral and cerebellar data might determine whether cerebellar data offers similar or distinct information regarding the relationship between brain activity and behavioral measures when compared to analyses of cerebral data.

4.3. Limitations

While providing novel evidence for associations between cerebellar hierarchical organization shown by fMRI and different dimensions of psychopathology, our analyses can provide only correlational – not causal – inferences between cerebellar function and behavior; future interventional experiments such as brain stimulation studies may be able to demonstrate not only an association but also a causal link between cerebellar function as indexed by functional gradients and behavioral measures. Another limitation that can be addressed in future research includes the relatively limited range of diagnostic categories in the patient population (ADHD, SZ, and BD); future research may extend our analyses to include additional patient populations. The analyses on the impact of medication and substance use were exploratory in our study; future studies with higher statistical power might adopt stronger statistical thresholds to study medication and substance use effects. In addition, because this dataset used in this study did not provide information of comorbidities in this cohort, we cannot evaluate the potential effect of comorbidities on the observed results. And, it should be acknowledged that the sample size for the CNP dataset is relatively small, especially for a multivariate analysis including thousands of variables. Meanwhile, considering there was about 0.1 drop from 0.16 to 0.27 to 0.07–0.16 in the terms of correlation between cerebellar gradient and behavioral composite scores in the test folds when ignoring diagnostic groups, we acknowledged that diagnostic groups may have a certain impact while this impact did not reach statistically significant level. This may arise from the limited diagnostic groups including in the

CNP cohort, which might lead to the discontinuity in terms of psychopathology. Future studies employed larger sample size and with more diagnostic groups would be helpful to replicate the observed dimensions. Although we used all the behavioral measures (N = 119) in the present study, only 55 measures mainly focused on the assessments of impulsivity, memory, and executive functioning were included in the PLS analysis when considering the availability of each measure for each subject, with some other measures such as psychosis and moods less represented. Such selection bias might influence the derived results. Future study would be helpful to replicate the derived results using dataset with broader assessments for psychopathology, which would also be helpful to more convincedly determine the name of each dimension.

5. Conclusions

Our results support an association between cerebellar functional connectivity gradients and multiple behavioral dimensions across healthy subjects and patients diagnosed with a variety of mental disorders. These findings highlight the importance of cerebellar function in transdiagnostic behavioral dimensions of psychopathology, and contribute to the development of cerebellar neuroscience as a tool that may significantly contribute to the study and classification of transdiagnostic dimensions of psychopathology. The present findings also call on researcher to pay more attention to the role of cerebellum in the dimensions of psychopathology, not just within the cerebral cortex.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data are freely provided by from the UCLA Consortium for Neuropsychiatric Phenomics (CNP) available from OpenNeuro (https://openneuro.org/datasets/ds000030/versions/00001).

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Appendix A. Supplementary data

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